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Relationship between presence of anticardiolipin antibodies and miscarriage

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Abstract:

This descriptive study was includes 58 patients with anticardiolipin antibodies were selected out of 290 female patients suffering from miscarriage. All patients were attending Al-Yarmok hospital department of obstetrics and gynecology during the period from 1/July 2015 to 30/April 2016.They were examined their blood and took the information and history in the data questionnaire forms. The data questionnaire designed for purpose of study after read the literatures review. The main goals of this study are evaluate the prevalence of anticardiolipin antibodies among women with miscarriage and to determine any association between anticardiolipin antibodies and other factors. The data were analyzed using frequency distribution and the percentage by using the computer software. The result of study include anticardiolipin antibodies 20% from all miscarriage patients, 71.4% anticardiolipin antibodies within first trimester, It was showed that incidence of anticardiolipin antibodies with miscarriage 66.07% of patients in the (15 -29) age group, It was showed incidence anticardiolipin antibodies 50% of patients with two miscarriage. 50% of patients with two miscarriage, 28.57% of patients with three miscarriage, illustrated the percentage of miscarriage due to the concentration level of anticardiolipin antibodies was (62.3%) patients in the (60-79) GPLU level. They were incidence of patients with anticardiolipin antibodies and other recurrent or chronic diseases. It is found 28.57% with urinary tract infection, 17.87% with autoimmune diseases, 5.36% with bacteremia, 1. 78% with viral infection, 7.14% respiratory tract infection, while 37.5% idiopathic. The study recommendation the women with one or recurrent miscarriage should be screened the anticardiolipin antibodies before pregnancy for correct assessment and investigations of couples with recurrent miscarriage. Put don't TORCH tests only to correct diagnosis and treatment and prevent miscarriage.

Introduction:

A- **Cardiolipin**: It is a kind of diphosphatidylglycerol lipid. Two phosphatidic acid moieties connect with a glycerolbackbone in the center to form a dimeric structure. [1] So it has four alkyl groups and potentially carries two negative charges. As there are four distinct alkyl chains in cardiolipin, the potential for complexity of this molecule species is great. However, in most animal tissues, cardiolipin contains 18-carbon fatty alkyl chains with 2 unsaturated bonds on each of them.[2] It can also be found in the membranes of most bacteria. The name 'cardiolipin' is derived from the fact that it was first found in animal hearts. It was first isolated from beef heart in the early 1940s. [1] Cardiolipin distribution to the outer mitochondrial membrane would lead to apoptosis of the cells. [2]

B- **Antibody** (Ab), also known as an immunoglobulin (Ig), is a large, Y-shaped protein produced mainly by plasma cells that is used by the immune system to identify and neutralize pathogens such as bacteria, viruses and others. The antibody recognizes a unique molecule of the harmful

agent, called an antigen, via the variable region. Antibodies can come in different varieties known as isotypes or classes known as IgA, IgD, IgE, IgG, and IgM. [3]

C- **Antigen**(Ag) is a molecule capable of inducing an immune response on the part of the host organism, [1] though sometimes antigens can be part of the host itself.The antigen may originate from within the body ("self-antigen") or from the external environment ("non-self"). The immune system usually does not react to self-antigens under normal homeostatic conditions due to negative selection of T cells in the thymus and is supposed to identify and attack only "non-self" invaders from the outside or modified/harmful substances present in the body under distressed conditions. [3]

Autoimmune disease:

Autoimmune disease occurs when the body's immune system acts against itself. Therefore, in the case of an autoimmune-induced miscarriages the woman's body attacks the growing fetus or prevents normal pregnancy progression.[4] Further research also has suggested that autoimmune disease may cause genetic abnormalities in embryos which in turn may lead to miscarriage.[5] As an example, Celiac disease increases the risk of miscarriage.[6]

Anti-cardiolipin antibodies (ACA):

The investigated to which degree of IgG, IgA and IgM anticardiolipin antibodies are associated with recurrent abortion. Anticardiolipin is a major cause of recurrent fetal loss and many pregnancies can be saved if diagnosed and treated adequately. High anticardiolipin antibody levels were identified in 55.77% . Patients with anti-cardiolipin antibodies (Antiphospholipid syndrome) can have recurrent thrombotic events even early in their mid- to late-teen years. [7] These events can occur in vessels in which thrombosis may be relatively uncommon, such as the hepatic or renal veins. These antibodies are usually picked up in young women with recurrent spontaneous abortions (miscarriages). In anti-cardiolipin-mediated autoimmune disease, there is a dependency on the apo-lipoprotein H for recognition.[4] Additional anti-cardiolipin diseases, infection by bacteria is a serious chronic bacterial infection shared by both cats and humans. [8]

Miscarriage:

It is also known as spontaneous abortion and pregnancy loss, is the natural death of an embryo or fetus before it is able to survive independently. Miscarriage had been always a problem for both, the doctors (gynecologists) and for the patients who are the pregnant women. [9] The most common symptoms of a miscarriage is vaginal bleeding with or without pain. This can vary from light spotting or brownish discharge to heavy bleeding and bright red blood. The bleeding may come and go over several days. Sadness, anxiety, and guilt may occur. Tissue or clot like material may also come out of the vagina. However, light vaginal bleeding is relatively common during the first trimester of pregnancy (the first 12 weeks) and does not necessarily indicate a miscarriage. Symptoms other than bleeding are not statistically related to miscarriage.[10] Abortion is the ending of pregnancy by removing a fetus or embryo before it can survive outside the uterus. An abortion which occurs spontaneously is also known as a miscarriage. The word abortion is often used to mean only induced abortions (termination of pregnancy). [11] The

miscarriage or spontaneous abortion occurs in the first trimester and second trimester of pregnancy. [9]

Recurrent miscarriage etiology:

Miscarriage may occur for many reasons, not all of which can be identified. Some of these causes include genetic, uterine, or hormonal abnormalities, reproductive tract infections, and tissue rejection autoimmune diseases.[12]

1- **First trimester etiology**:

Most clinically apparent miscarriages occur during the first trimester.[12] About 30% to 40% of all fertilized eggs miscarry, often before the pregnancy is known.[11] The embryo typically dies before the pregnancy is expelled. Although the prevalence of anticardiolipin antibodies is greater in patients with first-trimester losses.[12] Chromosomal abnormalities are found in more than half of embryos miscarried in the first 13 weeks;[12] Progesterone deficiency may be another cause. Those diagnosed with low progesterone levels in the second half of their menstrual cycle (luteal phase) may be prescribed progesterone supplements, to be taken for the first trimester of pregnancy.[13] There is no evidence that progesterone given in the first trimester reduces the risk of miscarriage, and luteal phase progesterone deficiency may or may not be a contributing factor to miscarriage.[13]

2- Second trimester etiology :

Second trimester losses may be due to uterine malformation, growths in the uterus (fibroids), or cervical problems. These conditions also may contribute to premature birth.[18] One study found that 19% of second trimester losses were caused by problems with the umbilical cord. Problems with the placenta also may account for a significant number of later-term miscarriages.[14]

3- Induced miscarriage etiology:

If a pregnant person does not want to give birth, doctors may induce a therapeutic abortion. In places where induced abortion is illegal or carries heavy social stigma, those who wish to end the pregnancy may attempt self-induced abortion, sometimes called "induced miscarriage" or "self-induced miscarriage".[15]

Risk factors of miscarriage:

1-Multiple pregnancy: Pregnancies with more than one fetus are at increased risk for miscarriage. This risk increases with the number of fetuses in the pregnancy.[12]

2- Inter current diseases: Several intercurrent diseases in pregnancy can potentially increase the risk of miscarriage, including diabetes, polycystic ovarian syndrome, hypothyroidism, certain infectious diseases, and autoimmune diseases. [16]

3- Hypothyroidism increases the risk of miscarriage. The effect of milder cases of hypothyroidism on miscarriage rates has not been established. The presence of certain immune conditions such as autoimmune diseases is associated with a greatly increased risk.[17] The presence of anti-thyroid autoantibodies is associated with an increased risk with an odds ratio .[17]

4- Diseases transmitted vertically (through the placenta to the fetus), such as rubella or chlamydia, can increase the risk of miscarriage.[18]Mycoplasma genitalium infection is associated with increased risk of preterm birth and miscarriage.[18]

5- Smoking: Tobacco (cigarette) smokers have an increased risk of miscarriage. There is an increased risk regardless of which parent smokes, though the risk is higher when the gestational parent smokes. [19]

6- Age: (Advanced maternal age) The age of the pregnant person is a significant risk factor. Miscarriage rates increase steadily with age, with more substantial increases after age 35.[20]

7- Morning sickness: Nausea and vomiting of pregnancy are associated with a decreased risk. Several proximate causes have been proposed for this relationship, but none are widely agreed upon, according to this model, a lower frequency of miscarriage would be an expected consequence of the different food choices made by a women experiencing Nausea and vomiting of pregnancy. [21]

8- Exercise: A study of more than 92,000 pregnant people found that most types of exercise (with the exception of swimming) correlated with a higher risk of miscarrying prior to 18 weeks. No relationship was found between exercise rates after the 18th week of pregnancy. [22]

9- Caffeine: Caffeine consumption also has been correlated to miscarriage rates, at least at higher levels of intake. However, such higher rates have been found to be statistically significant only in certain circumstances. A 2007 study of more than 1,000 pregnant people found that those who reported consuming 200 mg or more of caffeine per day experienced a 25% rate of miscarriage, compared to 13% among women who reported no caffeine consumption. [23]

10- Other: abnormal mass in the gestational sac, next to a normal embryo (at bottom right) of a gestational age of 7 weeks with visible heartbeat. Masses like these are presumed to increase the risk of miscarriage. Sexual intercourse during the first trimester has often been assumed by doctors to be a cause of miscarriage. However the association has never been proved or disproved. Cocaine use increases the rate of miscarriage.[29] Physical trauma, exposure to environmental toxins, and use of an intrauterine device at the time of fertilization have also been linked to increased risk. Antidepressants, especially paroxetine and venlafaxine, can cause a miscarriage. [24]

C- Miscarriage diagnosis:

1- Bleeding during early pregnancy is the most common symptom of both impending miscarriage.

2- A miscarriage may be confirmed via obstetric ultrasound and by the examination of the passed tissue miscarriage may be detected (diagnosis) during an ultrasound exam, or through serial human chorionic gonadotropin (HCG) testing...[25]

Treatment of anticardiolipin:

Treatment using heparin, aspirin or intravenous immunoglobulins reduces the rate of fetal loss.]. The reduction of these symptoms with the normalization of the levels of ACA is associated to an improvement in the survival rate of fetuses during pregnancy [26].

The main goals of this study are:

The study was evaluating the prevalence of anticardiolipin antibodies among women with miscarriage and to determine any association between anticardiolipin antibodies and other factors.

Defined of terms:

1- **Anticardiolipin antibodies**: It is consensus autoimmune diseases have a multifactorial aetiology, depending on both genetic and environmental factors. It is a immune response is a major reproductive complication in women, which is characterized by recurrent fetal loss, thrombosis, and thrombocytopenia in association when the body's immune system acts against itself. [4] [7]

2- **Miscarriage**: It is also known as spontaneous abortion and pregnancy loss, is the natural death of an embryo or fetus before it is able to survive independently. [9]

Method:

This is descriptive study includes 58 patients with anticardiolipin antibodies were selected out of 290 female patients suffering from miscarriage. All patients were attending Al-Yarmok hospital department of obstetrics and gynecology during the period from July 2015 to month, April 2016.They were examined their blood and took the information and history in the data questionnaire forms. The data questionnaire designed after read the literatures review for purpose of study. It is include age, number of miscarriage, period of miscarriage through the pregnancy, signs and symptoms, genetic factors, other chronic diseases, with do laboratory investigation include, anticardiolipin antibodies titer by ELISA technical and other laboratory tests were don. The prospective study was to detection the association between anticardiolipin antibodies and miscarriage through the pregnancy period. The data were analyzed using frequency distribution and the percentage by using the (Excel) computer software.

Result and discussion:

The study includes 58 patients with anticardiolipin antibodies were selected out of 290 patients' female suffering from miscarriage and pregnancy loss. Table (1) shows 20% of miscarriage woman has anticardiolipin antibodies without treatment, this rise slightly with the other study carried out in 1993 that is present anticardiolipin antibodies in 15% of women with recurrent miscarriage,[27] and other study carried out in 2010 high anticardiolipin antibody levels were identified in 55.77%. [7] This variation and arises as a result of the difference of environment, place, which may be contain etiology of the anticardiolipin antibodies compared to the environment of British, Iraq and Brazil. The culture about the disease as well as genetic factor might have effect or due to the different methods employed to measure the antibodies. The mechanisms by which anticardiolipin antibodies cause pregnancy morbidity include inhibition of trophoblastic function and differentiation, activation of complement pathways resulting in a local inflammatory response and thrombosis of the uteroplacental vasculature. In vitro studies have shown that the effect of antiphospholipid antibodies on trophoblast function and complement

activation is reversed by heparin. [28] To avoid the impact of the anticardiolipin antibodies on pregnant women used anticoagulants during pregnancy and even after pregnancy to avoid the thrombosis which develops with age and the presence of the causative.

Table (2) showed that the anticardiolipin antibodies 71.4% of patient with miscarriage were in the first trimester of pregnancy, 28.6% in the second trimester. This result disagrees with.[11] Who found Strongly elevated levels of IgGacl were detected in (30%) with recurrent abortions in the first trimester. The study was agreed with [12] that found prevalence of anticardiolipin antibodies is greater in patients with first-trimester losses. The mechanisms by which anticardiolipin antibodies cause pregnancy morbidity include inhibition of trophoblastic function and differentiation, activation of complement pathways at the maternal–fetal interface resulting in a local inflammatory response and thrombosis of the uteroplacental leading to loss of pregnancy.

The table (3), It was showed that incidence of anticardiolipin antibodies 66.07% of patients in the (15 -29) age group, 25% in the (30 -44) age group and low in the other. This is the age of marriage in Iraq and the rise in the percentage of patients suffering from miscarriage. They were obliged to review the hospitals and clinics for treatment and get the kids that were explaining the high number of patients from this topic age group. While the older age groups were less of them because they may have children after treatment or they were sense of hopelessness because they were failure to obtain the children or solved the problem by adoption of another child from outside the family, which is rare in the Middle East. The study does not conform to another study in Europe [29]. This variation was as a result of the adoption of age as a cause of abortion but not anticardiolipin antibodies causes. This variation is due to the different methods employed.

Table (4): It was showed incidence anticardiolipin antibodies 50% of patients with two miscarriages, 28.57% of patients with three miscarriage, and low percent in other. This appears interest the women suffering for repeat miscarriage, them to visit the hospital, clinics and overlooked mostly first miscarriage that may be the onset of the disease. Miscarriage that increases with the level of anticardiolipin antibodies with present causes of immune response that leads to thrombosis and close the blood vessels in the uterus and placenta. All women with recurrent of miscarriage should be screened before pregnancy for anticardiolipin , antiphospholipid antibodies, and correct assessment and investigations of couples with recurrent miscarriage to prevent loss of pregnancy and others complication .When we know association with later disease recurrent miscarriage in itself is associated with later development of coronary artery disease increased risk of mortality of 44%, 86%, and 50% for women with a history of 1, 2, or 3 miscarriages, respectively. [30].

Table (5) illustrated the percentage of miscarriage patients due to the concentration level of anticardiolipin antibodies was (62.3%) in the (60-79) GPLU level from all patients, (37.5%) in same concentration level with two time miscarriage, while (16.07%) of patients in (80-90)GPLU concentration level from all and low in others level . The study agree with [31] (reported a prevalence of these high level antibodies in from 15 to 59.1% of cases)and agreement with other study [7]that was reported (high IgM ACA levels were found in 41.1% of the cases. Abnormally high ACA levels were detected in 55.77% of the cases women). This little variation is according to the different methods employed to assay the antibodies or selective of patient was done by

other method. The high concentration level of anticardiolipin antibodies are effected the continuation of the pregnancy and cause the thrombosis lead to close the vessels and death of the fetus. To avoid a situation should be diagnosis and treatment the pregnant women.

Table (6) the illustrated that there was a relationship between incidence of patients with anticardiolipin antibodies and other recurrent or chronic diseases. It is found 28.57% with urinary tract infection, 17.87% with autoimmune diseases, 5.36% with bacteremia, 1. 78% with viral infection, 7.14% respiratory tract infection, while 37.5% idiopathic. Cardiolipin is an important component of the inner mitochondrial membrane, where it constitutes about 20% of the total lipid composition. It can also be found in the membranes of most microorganisms.
Any severe infection that leads to bacteraemia or viraemia can cause sporadic miscarriage. The role of infection in recurrent miscarriage is unclear. For an infective agent to be implicated in the etiology of repeated pregnancy loss, it must be capable of persisting in the genital tract and avoiding detection, or must cause insufficient symptoms to disturb the woman. [32] Toxoplasmosis, Rubella, cytomegalovirus, herpes and listeria infections do not fulfil these criteria and routine TORCH screening only should be abandoned. And the work of many investigations, especially anticardiolipin antibodies produce of changes and immune reactions because they are infection of various microorganisms.

Recommendation

1- All women with one or recurrent miscarriage should be screened before pregnancy for anticardiolipin antibodies Correct assessment and investigations of couples with recurrent miscarriage. Put don't TORCH tests only to correct diagnosis and treatment and prevent miscarriage.
2- Study the anticardiolipin antibodies of the subject on a large sample of patients.

Table (1): prevalence of anticardiolipin antibodies and percentage in the miscarriage patients.

anticardiolipin antibodies results	number	percentage
anticardiolipin (+ve)	56	20%
anticardiolipin antibodies (-ve) (other causes)	224	80%
Total	280	100%

Table: (2) The numbers and percent of patients with first and second trimester.

anticardiolipin and miscarriage through the period of pregnancy	number	percentage	C.S

first trimester	40	71.4%	P>0,05
second trimester	16	28.6%	
total	56	100%	

Table: (3) distribution umber and percentage of patients within the age groups.

age group (years)	number	percentage	C.S.
15 -29	37	66.07%	
30 -44	14	25%	P>0,05
45 -60	5	8,93%	
total	56	100%	

Table: (4) relationship between anticardiolipin antibodies and number of miscarriage:

number of miscarriage	number	percentage
one	8	14.29%
tow	28	50%
three	16	28.57%
four	4	7.14%
total	56	100%

Table (5) Relationship between anticardiolipin antibodies titer with number and percentage of miscarriage:

level anticardiolipin AB IgM (GPLU)	patients numbers with miscarriage and percentage									
	one	%	tow	%	three	%	four	%	total number	percentage
40 – 59	1	1.79%	3	5.36%	1	1.79%			5	8.93%
60 - 79	5	8.93%	21	37.5%	8	14.28	1	1.79%	35	62.5%

						%				
80 - 99		0%	1	1.79%	5	8.92%	3	5.36%	9	16.07%
100 -	1	1.79%	3	5.36%	2	3.57%	1	1.79%	7	12,5%
total	8	14,29%	28	50%	16	28.57 %	4	7.14%	56	100%

Table: (6) Disruption the number of patients with anticardiolipin antibodies to the others iseases.

Patients with other chronic diseases	number	percentage
Urinary tract infection	16	28.57%
Auto immune diseases. Rheumatoid arthritis, Allergy	10	17.86
Bacteremia, Typhoid, brucellosis..	3	5.36%
Viremia, Hepatitis B virus	1	1.785%
Respiratory tract infection, Tonsillitis, pneumonia..	4	7.14%
Epilepsy	1	1.785%
Idiopathic	21	37.5%
Total	56	100%

Refrence:

1- Nowicki, M. (2006). "Characterization of the Cardiolipin Synthase from Arabidopsis thaliana". Ph.D. thesis, RWTH-Aachen University.

2- Michael, S., Stuart, B., Karl, Y. (1993). "Mitochondrial cardiolipin in diverse eukaryotes". European Journal of Biochemistry 212 (3): 727–733.

3-Rhoades, R., Pflanzer RG (2002). Human Physiology. (4th ed.). Thomson Learning. p. 584.

4- Agarwal, K., Alfirevic Z. (2012). "Pregnancy loss after chorionic villus sampling and genetic amniocentesis in twin pregnancies: a systematic review.". Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology 40 (2): 128–34.

5- Gleicher, N., Weghofer A., Barad, D. (2007). "Female infertility due to abnormal autoimmunity: Frequently overlooked and greatly underappreciated. Part II". Expert Review of Obstetrics & Gynecology 2 (4): 465–75.

6- Gleicher N., Weghofer A., Barad D. (2011). "Do chromosomally abnormal pregnancies really preclude autoimmune etiologies of spontaneous miscarriages?". Autoimmunity Reviews 10 (6): 361–3.

7- Galão E., Bagarelli L., Oliani A. (2010). Prevalence of Anticardiolipin Antibodies in Pregnancies with History of Repeated Miscarriages: Open Rheumatol J. 4: 28–30.

8- Spinella A., Lumetti F., Sandri G., Cestelli V., Mascia M., (2012). Beyond cat scratch disease: a case report of bartonella infection mimicking vasculitic disorder. Case Rep Infect Dis.;2012:354625.

9- Lippincott W. & Wilkins. (2012). The Johns Hopkins Manual of Gynecology and Obstetrics: (4 ed.). pp. 438–439.

10-Robinson, G. (January 2014). "Pregnancy loss.". Best practice & research. Clinical obstetrics & gynaecology 28 (1): 169–78.

11- Kalra S., Tuli A., Choudhry R., Raheja S, (2003). " Prevalence of anticardiolipin antibody IgG in recurrent first trimester abortions and the role of aspirin in its prevention: Med Sci Monit. Jun; 9(6):CR213-6.

12- Carlos W., and et all. (2001). Anticardiolipin antibodies in first- and second-trimester pregnancy loss. Volume 97, Issue 4, Supplement 1, Apri.l P. S32.

13- Wahabi H., Fayed A., Esmaeil SA, Al Zeidan R., Wahabi, A. (2007). "Progestogen for treating threatened miscarriage". ed. Cochrane Database of Systematic Reviews (12):

14- Peng H., Levitin-Smith M, Rochelson B., Kahn E. (2006). "Umbilical Cord Stricture and Over coiling Are Common Causes of Fetal Demise". Pediatric and Developmental Pathology 9 (1): 14–9.

15- Oliver, A., Overton, C. (May 2014). "Diagnosis and management of miscarriage.". The Practitioner 258 (1771): 25–8,

16- Boomsma, C., Fauser, B., Macklon, N. (January 2008). "Pregnancy complications in women with polycystic ovary syndrome.". Seminars in reproductive medicine 26 (1): 72–84.

17- Boogaard, E. and et all. (2011). "Significance of (sub) clinical thyroid dysfunction and thyroid autoimmunity before conception and in early pregnancy: A systematic review". Human Reproduction Update 17 (5): 605–19.

18- Lis, R.; Rowhani-Rahbar, A., Manhart, L. E. (2015). "Mycoplasma genitalium Infection and Female Reproductive Tract Disease: A Meta-Analysis". Clinical Infectious Diseases 61: 418–26.

19- Venners, S. and et all. (2004). "Paternal Smoking and Pregnancy Loss: A Prospective Study Using a Biomarker of Pregnancy". American Journal of Epidemiology 159 (10): 993–1001.

20-Bray, I., Gunnell D., Davey, G. (2006). "Advanced paternal age: How old is too old?". Journal of Epidemiology & Community Health 60 (10): 851–3.

21- Furneaux, E., Langley-Evans A., Langley, S. (2001). "Nausea and Vomiting of Pregnancy: Endocrine Basis and Contribution to Pregnancy Outcome". Obstetrical and Gynecological Survey 56 (12): 775–82.

22- Madsen, M. and et all. (2007). "Leisure time physical exercise during pregnancy and the risk of miscarriage: A study within the Danish National Birth Cohort". BJOG 114 (11): 1419–26.

23- Weng, X., Odouli, R. (2008). "Maternal caffeine consumption during pregnancy and the risk of miscarriage: a prospective cohort study". Am. J. Obstet. Gynecol. 198 (3): 279.e1–8.

24- Nakhai H., Broy, P., Bérard, A. (2010). "Use of antidepressants during pregnancy and the risk of spontaneous abortion". Canadian Medical Association Journal 182 (10): 1031–7.

25- Yip, S., Sahota, D., Cheung, L., Lam, P., Haines, C., Chung, T. (2003). "Accuracy of Clinical Diagnostic Methods of Threatened Abortion". Gynecologic and Obstetric Investigation 56 (1): 38–42.

26- Salazar-Paramo, M., et all. (2002) Longitudinal study of antinuclear and anticardiolipin antibodies in pregnant women with systemic lupus erythematosus and antiphospholipid syndrome. Rheumatol Int. 22(4):142–7.

27- Pattison, N.,Chamley, L., McKay, E., Liggins, G.,Butler, W. (1993). Antiphospholipid antibodies in pregnancy:prevalence and clinical association.Br J Obstet Gynaecol 100:909–13.

28- Miyakis, S., et al. (2006). International consensus statement on an update of the classification criteria for definite antiphospholipid (APS). J Thromb Haemost 4:295–306.

29- Rochebrochard, E.,Thonneau, P. (2002). Paternal age and maternal age are risk factors for miscarriage; results of a multicentre European study.*Hum Reprod*;17:1649–56.

30- Oliver-Williams, C., Heydon, E., Smith, G., Wood, A. (2013). "Miscarriage and future maternal cardiovascular disease: A systematic review and meta-analysis". Heart 99 (22): 1636–1644.

31- Spegiorin, L., Godoy, J., Oliani, A.(2007).Evaluation of prophylaxis using low doses of heparin associated with aspirin in pregnancy with multiple miscarriages and high antiphospholipid antibody levels. Arch Med Sci. ;3:43–45.

32- Regan, L., Jivraj S. (2001). Infection and pregnancy loss. In: MacLean, AB, Regan L, Carrington D, editors. Infection and pregnancy. London: RCOG Press; p. 291–304.

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